DTU Library

Control banding tools for occupational exposure assessment of nanomaterials - Ready for use in a regulatory context?

Liguori, Biase; Hansen, Steffen Foss; Baun, Anders; Jensen, Keld Alstrup

Published in:
NanoImpact

Link to article, DOI:
10.1016/j.impact.2016.04.002

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

NanoImpact 2 (2016) 1–17

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.journals.elsevier.com/nanoimpact

Control banding tools for occupational exposure assessment of nanomaterials — Ready for use in a regulatory context?

Biase Liguori [a,b], Steffen Foss Hansen [a], Anders Baun [a], Keld Alstrup Jensen [b,*]

[a] DTU Environment, Technical University of Denmark, Building 113, Kgs. Lyngby DK-2800, Denmark
[b] National Research Centre for the Working Environment, Lersø Parkallé 105, DK-2100 Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 4 April 2016
Accepted 4 April 2016
Available online 16 April 2016

Keywords:
Nanomaterials
Control banding
Exposure estimation
Risk assessment
Risk management

ABSTRACT

The development, production and application of engineered nanomaterials are becoming more and more widespread. Because researchers, developers and industrial workers are the first in line to be exposed to potentially hazardous nanomaterials, appropriate occupational exposure assessment is a key area of concern. Therefore, a number of Control Banding (CB)-based tools have been developed in order to assess and manage the potential risks associated with occupational exposure to nanomaterials.

In this paper we provide a comparative analysis of different nanomaterial-specific types of control-banding/risk prioritization tools (the Control Banding Nanotool, IVAM Technical Guidance, Stoffenmanager Nano, ANSES CB Tool, NanoSafer, and the Precautionary Matrix) in order to evaluate their use-domains; types, extent, use and availability of input parameters; their output format; and finally their potential use and maturity in regard to meeting the minimum requirements for occupational exposure assessment under REACH and the conceptual source-transmission-receptor model by Schneider et al. (2011). This was done through an analysis including a literature review and use of the tools.

It was found that the tools were developed for different purposes, with different application domains and inclusion criteria. The exposure assessments and derived risk levels are based on different concepts and assumptions and outputs in different formats. The use of requested input parameters for exposure assessment differ greatly among the tools. Therefore, direct inter-comparison and combination of the different models into a larger holistic framework is not immediately possible.

Harmonization of input parameters and output could allow establishment of an exposure assessment framework with different levels of information requirements.

1. Introduction

The development, production and application of manufactured nanomaterials (NM)[1] have increased fast in different fields in recent years. The growth in industrial use and application of NM can be expected to lead to increased occupational exposure incidents to NM. At the same time, it has been recognized that NM may possess different toxicological profiles and exposure characteristics due to their nm-scale and particular reactivity as compared to that of the same compound in the μm-scale (Oberdörster, 2002; Oberdörster et al., 2005; Warheit, 2008; Warheit et al., 2008; Karlsson et al., 2009; Bakand and Hayes, 2012; Schulte et al., 2013). It is currently impossible to generate sufficient hazard data case-by-case at the same pace as the technological development and implementation of nanomaterials occur (WHO/EURO, 1985; Linkov et al., 2009; SCENIHR, 2010). For exposure assessment and risk management the lack of data is even more pronounced than for hazard (Safe Work Australia, 2010; Maynard, 2014; Seipenbusch, 2014a). Even-though, considerable efforts has already been made to establish inhalation exposure scenarios with contextual information (Seipenbusch, 2014a) and exposure measurement databases for risk assessment purposes (PEROSH, 2014), these data resources are still far from complete and rarely give results on the specific NM exposure. This is because it normally requires a highly dedicated study to quantify the specific NM-exposure in workplace measurements due to mixture with other particle sources in the factory, as well as aerosol dynamics

* Corresponding author.
E-mail address: kaj@nrcwe.dk (K.A. Jensen).

[1] In this paper with term manufactured 'nanomaterial' we principally refer to the EC recommendation (EC 2011); and in particular highlight point 1: "*'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, have one or more external dimensions is in the size range* 1 nm–100 nm"; and point 5: "*In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%*". However once we refer to the tools and other authors, other terms may be used which have been adopted by tools but can diverge from the EC recommendation.

http://dx.doi.org/10.1016/j.impact.2016.04.002
2452-0748/

including agglomeration and deposition (Asbach et al., 2014; Seipenbusch, 2014a, 2014b). There is a growing number of studies documenting the protective efficacy for nanomaterials of engineered and personal protection equipment (Rengasamy et al., 2004; Dolez et al., 2009; Shaffer and Rengasamy, 2009; Park et al., 2011; Faccini et al., 2012; Koivisto et al., 2015), however information on the efficacy of industrial solutions is still scarce. Therefore, it will normally be impossible to complete occupational exposure estimations from standard workplace measurements and read across from analogous data as they are outlined in e.g., the technical guidance documents provided by the European Chemical Agency (ECHA) (Jensen et al., 2010; Aitken et al., 2011; Hankin et al., 2011; ECHA, 2012a).

In the absence of reliable exposure measurement data, the ECHA Guidance R.14 suggests that Tier 1 and Higher Tier tools can be used to perform an alternative exposure assessment. The Tier 1 tools mentioned include ECETOC TRA (Targeted Risk Assessment), MEASE (Metals-EASE), and the EMKG-Expo-Tool (Einfaches Maßnahmenkonzept für Gefahrstoffe) and are considered to provide worst case exposure estimates based on a limited number of input data (see Supplementary material, Table S1). The Higher Tier tools: RISKOFDERM, Stoffenmanager, and the Advanced REACH Tool (ECHA, 2012a) enable quantitative exposure estimates with a higher number of input data (see Supplementary material, Table S2). Tier 1 tools are relatively simple and inherently conservative and best used for initial screening (ECHA, 2012a). The higher Tier tools are proposed when the assessments from Tier 1 tools indicate excessive exposure levels. However, all the tools mentioned in R.14 (ECHA, 2012a) have important limitations when it comes to exposure and risk assessment of NM and consequently potentially provide inadequate background for risk assessment.

First, to complete the assessment, all the REACH tools require an occupational exposure limit (OEL) or similar values, which only exists for a few specific NM. Alternatively, experimental values such as no-observed-effect-levels (NOEL) or lowest-observed-effect-levels (LOEL) may be used. Establishment of such alternative data requires knowledge from epidemiological studies (not existing or not available), human exposure studies (insufficient knowledge), or interpretation from animal studies. Even-though toxicological data are available on several NM, the end-points studied so far with identification of a LOEL or NOEL are limited. Almost no data are available on carcinogenicity, mutagencity, allergenicity, and reprotoxicity of NM, which are the most critical end-points for risk identification and exposure management.

Second, there are limitations in the types of materials for which assessments can be made using REACH tools as well as in the physico-chemical properties and exposure parameters that are taken into consideration. In the EMKG-Expo and Stoffenmanager tool, the dustiness (scores) is predefined depending on types of material or their mistiness and physical characteristics (e.g., solid particles, firm granules or flakes, granules or flakes, coarse dust, fine dust, fine light powders, extremely dusty products). These categories do not seem to agree well with variability observed for nanomaterial powders and the process-specific release potentials for NM. Experimental evidence from testing in rotating drum and continuous drop systems show rather large variations ranging according to EN 15051 (BS EN 15051, 2006) from low: 10 mg/kg to higher than 250 mg/kg for different nanopowders (Dahmann et al., 2007; Schneider and Jensen, 2008; Jensen et al., 2009; Burdett et al., 2013; Levin et al., 2014). The ECETOC TRA and ART on the other hand enable use of test or default (not ECETOC TRA) dustiness values, which opens up for a wider dynamic range. Regarding materials, neither Stoffenmanager nor ART can be used for fibrous materials. As a note, it is worth mentioning that none of the Tier 1 tools have been validated before inclusion in the REACH guidance documents even-though validation is now in process for some of the tools (ETEAM Conference, 2014).

Third, the REACH models/tools require modification to enable exposure assessment of NM by taking into account additional information and considerations as concluded in the REACH Implementation Projects on Nanomaterials; RIPoN 2 (Hankin et al., 2011) and RIPoN 3 (Aitken et al., 2011). For hazard assessment, RIPoN-2 indicated that particle shape; surface area; surface energy; surface chemistry; surface charge; redox potential; cell-free ROS (reactive oxygen species) production capacity; as well as state of dispersion and state of agglomeration should also be taken into account. RIPoN-3 additionally outlined that for exposure assessment, discrimination of background particles; collection and analysis of size information as well as the effective high spatial and temporal variability; choice of metrics and measurement instruments; measurement of high aspect ratio nanomaterials; the number concentration, the surface area concentration should also be taken into consideration for exposure assessment. Yet, due to technological limitations, there are still some major developments of measurement technologies and protocols needed before such new metrics can be considered reliable and suitable for administrative use (Asbach et al., 2009; Leskinen et al., 2012; Levin, 2015; Levin et al., 2015a, 2015b). Given the lack of data; no nanomaterial-specific OEL; access to only a limited number of reliable measurement data; and the number of nano-specific information demands required in addition to those already requested in existing REACH exposure assessment tools, it is evident that approaches are urgently needed to enable assessments of the potential exposure and hazard of specific NM.

Control Banding (CB) tools represent such alternative approaches for risk management based on combined “computational” hazard and exposure ranking. Control Banding is defined as a generic pragmatic approach that can be used for the control of the workplace exposure to agents with unknown or uncertain toxicological properties and for which there is a lack of quantitative exposure estimations. For risk management, CB tools normally propose a range of control measures (such as general ventilation, and containment) according to the estimated range or “band” of hazard and the range or “band” of exposure” (ISO/TS 12901-2, 2014).

A number of CB-type tools have already been developed for NM. Currently these NM-specific Control Banding tools are primarily made for assessment and control of occupational airway exposure, which is also the current key priority in general risk management of NM (Stone et al., 2014). As already stated by Brouwer (2012), these CB-type tools have been made for different uses and have different levels of complexity. However, so far these tools have not been investigated and compared in detail, which is important to improve our understanding on how they differ in application domains as well as the types of assessments and information provided and potential improvements in future developments.

In this paper, we first introduce and analyze six CB-types of tools (or models) with respect to their application domains, input data requirements, and methods for estimation of exposure and hazard potentials, their output and final control. We compare the needed inputs in the CB tools with the requested information for exposure assessment under REACH as described in ECHA Guidance R.14 (ECHA, 2012a) and Appendix R14-4 (ECHA, 2012b), and the conceptual source to receptor exposure model by Schneider et al. (2011). A better understanding of the needed assessment parameters and calculation principles will enable a better foundation to assess their respective maturity and potentials for further development into administrative tools. Finally, we provide recommendations on the further development on CB-tools, harmonization and validation in order to improve the applicability and predictions made by most tools.

2. Models and Analyses

Six risk categorizations and CB-tools and methods were selected in the analysis: The Control Banding Nanotool; the IVAM Guidance; the Precautionary Matrix; Stoffenmanager Nano; the ANSES tool; and NanoSafer. A brief summary of each of these tools and methods is given below and in Table 1 with respect to their application domains, number of requested inputs, and types of output format.

Table 1
Key information and application domains of the Control Banding tools considered in this study.

Name	NM Definition (Ref)	Target group/scope	Number of total input parameters asked	Number of input parameters used			Number of control bands			"Outcome" RM recommendation	Ref.
				Nano-relevance	Hazard scaling	Exposure scaling	Haz.	Exp.	Risk		
CB Nanotool	ASTM[a] (1)	Nanotechnology researchers/ Risk assessment and management	45	–	15	5	4	4	4	Risk Level (RL). General recommendations.	Paik et al. (2008); Zalk et al. (2009) .
IVAM Guidance	Own (2) definition with some extend similar to EC[b] (3)	Workers/Occupational hygiene	27	–	2	1	3	3	3	Control level bands. General recommendations and reference to hierarchic Occupational Hygiene.	Cornelissen et al., (2011)
Swiss Precautionary Matrix	ISO/TS 27687[c] (4)	Employees, consumers and the environment/ Source identification and risk reduction	28	7	6	6	n.a.	n.a.	2	Need for action/no action	Höck et al. (2008); Höck et al. (2011); Höck et al. (2013).
Stoffenmanager Nano	ISO/TS 27687[c] SCENIHR. (2010)[d] (5)	Employers and employees/ Prioritize health risks and implementation of control measures.	47	–	2	26	5	4	3	Risk priority bands. Ranking priority of needed actions	van Duuren-Stuurman et al., 2012
ANSES CB Tool	ISO/TS 27687[c] EC[b]	Small to large enterprises/Exposure prevention	10	1	5	3	5	4	5	Control level (CL). Technical solutions for exposure prevention at work station	Ostiguy et al., 2010; Riediker et al., 2012
NanoSafer	ISO/TS 27687[c] EC[b]	SMEs/Precautionary risk assessment	29	5	5	13	4	5	5	Risk Level (RL). Recommendation and actions to be taken into consideration	Kristensen et al. (2010). Jensen et al. (in prep.)

a) ASTM International, 2007; b) European Commission, 2011; c) ISO, International Organization for Standardization, 2008; d) SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks, 2010;

(1) *ASTM - definition*
As nanotechnology is a rapidly developing field, it will be necessary to continually reassess the terms and definitions contained in this standard, for purposes of revision when necessary. The intent of the terms and definitions in this standard is to describe "...materials containing features between approximately 1 and 100 nm and to differentiate those properties different from properties found in either molecules or the bulk (interior) of larger, micron-sized systems."

(2) *IVAM - definition*
A nanoparticle is a particle with three dimensions in the range of 1 – 100 nm. A fibrous particle does have two dimensions in the nano range of 1 – 100 nm

(3) *ISO/TS 27687 - definition*
Nano-object: Material confined in one, two, or three dimensions at the nanoscale. This includes nanoparticles (all three dimensions in the nanoscale), nanofibres (two dimensions in the nanoscale) and nanoplates (one dimension in the nanoscale). Nanofibres are further divided into nanotubes (hollow nanofibre), nanorods (solid nanofibre) and nanowire (electrically conducting or semiconducting nanofibre).

(4) *EC - definition*
Nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.

(5) *SCENIHR - definition*
Nanomaterial: Any form of a material that is composed of discrete functional parts, many of which have one or more dimensions of the order of 100 nm or less

2.1. Models

2.1.1. The control-banding nanotool — CB nanotool

The CB Nanotool was intended to enable precautionary qualitative risk assessment to protect researchers at the Lawrence Livermore National Laboratory (Paik et al., 2008; Zalk et al., 2009; Zalk and Paik, 2010). The CB Nanotool is available on the internet as a downloadable excel sheet model (http://www.controlbanding.net/). It is a simplified approach for experts and non-experts and accounts for factors determining the extent to which employees may be potentially exposed to nanomaterials. The CB Nanotool allocates 4 bands for hazard (severity score) and 4 bands for exposure (probability score) and 4 risk level control bands. The overall level of risk and corresponding control band is determined by a matrix arranged with the probability scores in the columns and the severity scores in the rows. The maximum probability/severity score is 100.

2.1.2. IVAM Guidance

The IVAM Guidance (Cornelissen et al., 2011) was developed in collaboration between employers and employees to provide a guidance to work safely with engineered NM and end-products. The method and guidance document is available from the internet (http://www.industox.nl/Guidance%20on%20safe%20handling%20nanomats&products.pdf). The system has a list of ten generic default activities to help the user in making an inventory of potential nanomaterial release along the life cycle. It allocates 3 bands for the hazard ranking, 3 bands for the exposure ranking, and 3 control level bands. The control level bands are classified in three control level A, B, C ranking from A lowest to C highest with corresponding advice for control measures for each control level.

2.1.3. Stoffenmanager Nano

Stoffenmanager Nano (van Duuren-Stuurman et al., 2012) is a nano-specific module supporting the generic Stoffenmanager risk-banding tool for assessment of NM during synthesis, in powders, sprays and embedded in products. It was developed by TNO and ArboUnie, Holland and is available as web-based tool (https://nano.stoffenmanager.nl/). The Stoffenmanager Nano tool is developed as a practical approach for employers and employees for risk prioritization in exposure situations where quantitative risk assessment is currently not possible. Stoffenmanager Nano can assess the risk both excluding and including risk management measures such as local exhaust ventilation and personal protection equipment. Stoffenmanager Nano allocates 5 bands for hazard, 4 bands for exposure and 3 for control banding. In the publication (van Duuren-Stuurman et al., 2012), the control bands are classified in three priority bands corresponding to low/medium/high priority of action. In the web-tool, the system gives the user a risk prioritization for the task and the "risk time" taking both duration and frequency into account.

2.1.4. ANSES CB nanotool

The ANSES CB nanotool was developed by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) to be applied for conducting risk assessment and risk management of work with manufactured nanomaterials or nano-enabled products in industrial settings (Ostiguy et al., 2010; Riediker et al., 2012). The method and guidance document is available from the internet (https://www.anses.fr/en/content/anses-proposes-innovative-approach-prevention-occupational-risks-nanomaterials). ANSES applies 5 hazard bands, 4 exposure bands (emission potential) and 5 control bands for risk. The control bands (levels) are derived by combinations of the hazard and exposure (emission potential) bands in a two-dimensional decision matrix, ranking from lower CL1 to higher CL5 associated with general recommendations.

2.1.5. NanoSafer

The NanoSafer CB-tool (Jensen et al., in preparation; Kristensen et al., 2010) was developed primarily for assisting small and medium-size companies and laboratories with no or limited experience in producing or working with nanomaterials and/or with insufficient resources to perform a full precautionary risk assessment. The system was initially developed for assessment of powder handling and fugitive/point-source emissions. The NanoSafer is available as a web-tool (http://nanosafer.i-bar.dk/Default.aspx). In NanoSafer, 4 bands are allocated for the hazard, 5 bands for exposure and 5 risk levels (control bands). Each control band (risk level) is associated with general recommendations for risk management and action that should be taken into consideration. It also contains an e-learning tool with inspiration on how to reduce exposure or risk thereof.

2.1.6. The Swiss Precautionary Matrix 3.0

The Swiss Precautionary Matrix is a risk categorization tool and cannot be properly categorized as a "conventional" Control Banding-based tool. However, it has some interesting concepts that are relevant for comparison with CB tools. The Swiss Precautionary Matrix is available through the internet and can be downloaded as a stand-alone tool (http://www.bag.admin.ch/nanotechnologie/12171/12174/14653/index.html?lang=en). It was developed by the Swiss Federal Office of Public Health and Federal Office for the Environment (Höck et al., 2008, 2011, 2013) and intends to help trade and industry producing or using nanomaterials and nano-enabled products to identify possible sources of risk from production, use and disposal; considering workers, consumers and the environment. The outcome is a score that can be smaller or greater than 20; if the outcome is greater than 20, the Precautionary Matrix suggests a need for action.

2.2. Analysis

The CB tools were compared in regard to a) scope and application domains; b) input parameters and their use; c) banding allocation and scaling principle, d) their determinant parameters for exposure evaluation, and e) their maturation levels as determined by to which extent they consider the minimum requirements for exposure assessment in the Technical REACH Guidance (ECHA, 2012a) and the conceptual Source-Transport-Receptor model for nanomaterial exposure assessment by Schneider et al. (2011).

For the Precautionary Matrix, Stoffenmanager Nano and NanoSafer tools, the analysis is based on available publications, disseminations, and on their web-based application. For the CB Nanotool, the literature description and its operational spreadsheet were the foundation for the analysis, and for the IVAM Guidance and the ANSES tools the evaluation was based only on their literature description.

It should be noted that in order to evaluate the general inputs of the tools and their control-banding banding principles, it was necessary to also consider the input parameters for hazard assessment, which encompasses: physico-chemical properties and material characterization, and relevant toxicological data.

3. Results

3.1. Scope and application domains

It is evident from the scope of each of the tools that they were developed for different purposes (Table 1). While the CB Nanotool was developed for protecting nanotechnology researchers, the IVAM Guidance was developed to support employers and employees in identifying the risks associated with different work situations, Stoffenmanager Nano, NanoSafer, and the ANSES tool were developed for occupational risk assessment and management during synthesis and downstream use of NM, but also laboratory work, and the Precautionary Matrix was developed for risk identification and prioritization considering the workplace, consumers and the environment in a life cycle perspective. None of the tools were developed considering REACH requirements. Therefore, compliance with the technical guidance documents prepared by ECHA is not a decisive quality criterion for the tools, but will be discussed later in regard to their potential regulatory use.

The primary nanomaterial inclusion criteria for using the tools are one of the key issues for comparison of the use domains. In this respect, all of the European tools, but the Swiss Precautionary Matrix, considers nanomaterials according to ISO/TS 27687 (ISO/TS 27687, 2008), which defines manufactured nano-objects (MNOs) as a material with one, two or three external dimensions in the nanoscale size-range; being approximately 1 to 100 nm, as well as their agglomerates and aggregates. This is also the basis for the number-based definition of a nanomaterial proposed by the European Commission in 2011, where a nanomaterial is a material where more than 50% by number of the manufactured nano-objects have a minimum diameter between 1 and 100 nm ((EC European Commission, 2011)). The Swiss Precautionary Matrix, acknowledges the nanomaterial definition, but includes materials consisting of objects with particle sizes up to 500 nm considering the biological properties. The US CB Nanotool defines the nanomaterial according to ASTM International (ASTM E2456, 2012) (formerly known as the American Society for Testing and Materials), which defined nanoparticles as having two or three dimensions < 100 nm.

For inclusion as a nanomaterial, the Precautionary Matrix, Stoffenmanager Nano, ANSES and NanoSafer also takes the specific surface area (SSA) into account. This metric was also proposed in the recommendation for a nanomaterial definition by European Commission (EC European Commission, 2011). For the Precautionary Matrix, SSA is an input parameter used to consider the nano-relevance. Stoffenmanager Nano includes materials with a SSA of 60 m^2/g or higher as an alternative to particle size. However, to follow the EC recommendation exactly, this value should in fact be the volume-specific surface area (VSSA) with a threshold value of 60 m^2/cm^3. NanoSafer deviates from the EC-recommendation on the VSSA for precautionary reasons and includes NM with VSSA greater than 30 m^2/cm^3.

3.2. Input parameters

As summarized in Table 1, the CB tools differ greatly in regard to the number of input parameters requested for the hazard- and the exposure assessment and final scaling (Table 1). Even-though they all consider the same key elements, the models have important differences in the specific phrasing of the specific requested input and in how the different input parameters are used in the respective models. This is illustrated in Tables 2 to 6, where the inputs have been sorted into the five Tables in accordance with the five groups of input categories defined in ISO/TS

12901-2:2014 (ISO/TS 12901-2, 2014): *Information and identification*; *Physicochemical properties and material characterization*; *Toxicology data*; *Exposure characterization*; *Characterization of control measure*. The specific questions and use of these data are further elaborated below in Sections 3.2.1 to 3.2.5.

It should be noted that in some models, the same input parameters may be used to determine both the nano-relevance (i.e., should it be considered a nanomaterial within the scope of the tool?) and the hazard or exposure. In Table 1 such parameters are counted twice. In any case, Tables 2 to 5 clearly demonstrate that the number of input parameters requested often is much higher than the number of parameters applied in the models. In the CB Nanotool, only 20 out of 53 requested input parameters are used for the allocation of the hazard-(Severity Score) and exposure bands (Probability Scores). In the IVAM Guidance tool, only 3 out of 28 input parameters are requested in the model. The ANSES tool only has 9 inputs that are used to determine the hazard and exposure bands.

The NanoSafer and Stoffenmanager Nano have much higher information requirements and ask for 25 and 47 entries, respectively. Two of the inputs on the NM identification in NanoSafer are optional and offered for the user to name and identify their registered NM for subsequent use. Including naming of the activity in NanoSafer, 23 of the 29 possible entries are used for allocation of the final risk level and 6 inputs are used for naming the material and work process. In Stoffenmanager Nano only 28 out of the 47 inputs are used to determine the hazard and the exposure, (2 and 26 respectively) and 19 are used for naming the material, for naming the work process and for preliminary decision tree questions to determine the toxicity of the material. In the Precautionary Matrix the input information consists of 28 entries. Besides general information inputs (e.g. on the responsible contact person, the description of the considered nanospecific field, the process information on the life cycle and uncertainties), 19 of the 28 input parameters are used in the assessments. Below we discuss in greater detail the information requirements considering the elements in ISO/TS 12901-2:2014 (ISO/TS 12901-2, 2014) to obtain further insight into the different thoughts behind the scope and assessments made by the different models,

3.2.1. Information and identification

Some of the tools specifically ask for the material name as well as CAS number and/or EINICS number as *Information and identification* input parameters. For identification, the Precautionary Matrix, Stoffenmanager Nano and the ANSES tool in addition to the "material or product name" also asks questions considering whether the material can be defined as nanomaterial according to ISO and EU definitions or whether the material is soluble or insoluble in water or whether it is a persistent fiber. In NanoSafer the nanorelevance of the material and type of nano-object is evaluated automatically based on the associated material descriptors and the physico-chemical input data on sizes, the VSSA (calculated from the specific gravity and the specific surface area), and solubility (see further discussion below). Similar approaches have recently been suggested for nanomaterial grouping and read-across (e.g., Oomen et al., 2015).

3.2.2. Physico-chemical properties and material characterization

There is a lot of similarity between the tools considering their requested physico-chemical properties and material characterization (Table 3). All tools ask for information on dimensions of the nano-objects and often information on reactivity in some form. The size-information is generally used to identify whether the material is a NM, but some size-information questions on e.g., level of agglomeration are also used for hazard assessment in the Precautionary Matrix.

All CB tools also consider the NM solubility or stability and some use this parameter as a screening element to determine whether the NM could be assessed using conventional risk assessment tools. The

Table 2
Overview of the specific information and identification requirements of the different CB tools analyzed. Shaded cells indicate that the specific information is not requested.

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Program[£]	–					
Activity number[£]	–					
Location of work[£]	–					
Responsible person contact info[£]	–					
Name of material (indicate CAS number and/or attach MSDS if applicable)[£]	–					
Nanomaterial vendor name and contact information (if applicable)[£]	–					
Benefits of application[£]	–					
Intended downstream use[£]	–					
Safe handling information available?[£]	–					
Scenario description (free text) [$]	–					
Current engineering control [$]	–					
Product name		–				
Chemical name		–				
CAS registration number		–				
Physical state of the nanomaterial (liquid or solid)		–				
Precautionary matrix completed by / responsible contact person			–			
Brief description of the considered nanospecific field (type of nanomaterials, which surrounding, in which application)			–			
Brief description of the considered (process) step (production, packaging, transport, further stages of processing, disposal, use...), brief description			–			
Scenario: Calculation of the precautionary need - for employees - for consumers -for a specific disposal step			–			
Material consists of fullerenes, graphene flakes or single wall nanotubes			N			
Is the origin of the (nanoscale) starting materials known?			I			
Is sufficient information available to complete the precautionary matrix for nanoscale starting materials?			I			
Are the subsequent users of the considered nanomaterials known?			I			
How accurately is the material system known, or can disturbing factors (e.g. impurities) be estimated?			I			

(continued on next page)

Table 2 (*continued*)

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Information and identification						
Name risk assessment €				–		
Source domain (Handling of bulk aggregated/agglomerated nanopowders; Release of primary particles during actual synthesis; Spraying or dispersion of a ready-to-use- nanoproduct; Fracturing and abrasion of MNO-embedded and prodcuts)€				E		
Product type€ (*Choose from selection*: Intermediate; Ready-to-use-product) [if source domain: Spraying or dispersion of ready-to-use nanoproduct]				X		
Product name€				–		
Supplier				–		
Date PIS (Product Information system)				–		
Date MSDS (Material Safety Data Sheet)				–		
Product appearance € (*default:* Powder) [Handling of bulk aggregated/agglomerated nanopowders]				X		
Product appearance (*Choose from selection:* Powder, Granules/flakes, Paricles dispersed in a liquid)€ [if source domain: Spraying or dispersion of ready-to-use nanoproduct]				X		
Product appearance€ (*Choose from selection*: Granules/flakes; Particles dispersed in a liquid) [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [Intermediate]				X		
Product appearance€ (*default*: Particles dispersed in a liquid)[if source domain: Spraying or dispersion of ready-to-use nanoproduct] [Ready-to-use-product]				X		
Name nano compound€				–		
Do you know the exact concentration of the nano component in the product? (Yes/No)€				E		
Exact concentration percentage (If you selected 'yes' in the option 'Do you know the exact concentration of the nano component in the product?')€				E		
Chose the concentration (If you selected 'No' in the option 'Do you know the exact concentration of the nano component in the product?' Choose from selection: Pure product (100%); Many Component (50-99%); Substantial (1-10%); Very small (0.01-1%); Extremely small <0.01%)€				E		
Information and identification						
Do you know the exact dilution of the product with water? (Yes/No)€ [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [Particles dispersed in a liquid]				E		
Exact percentage (If you selected 'yes' in the option 'Do you know the exact dilution of the product with water?')€ [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [Particles dispersed in a liquid]				E		
Dilution with water: (If you selected 'no' in the option 'Do you know the exact dilution of the product with water?' Choose from selection: Undiluted; Concentrated; Moderately diluted; Diluted; Very diluted; Extremely diluted)€ [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [Particles dispersed in a liquid]				E		
				E		
Does the product contain fibers/fiber like particles? (Yes/No)€				X		
Does the product contain nanomaterials?					N	
Is the nanomaterial already classified by relevant authority?					H	
Material						–
Producer						–
What is the material CAS number?						–
What is the material EINECS number?						–
Is the material is labeled with one of the following words ? Nano, Dot, Cluster, Fullerene, Fulleroid, Fullerol, Quantum, Organoflake, Organoclay, Nanotube, Dendrimer, Ultrafine						N

N: Nano relevance; H: Hazard scaling; E: Exposure scaling; I: Available Info/Uncertainty; X: decision tree preliminary questions; --: input not used for the assessment. £: Nanomaterial Field-Information Form for CB Nanotool; $: Spreadsheet entry for Control Banding Tool Version2 6-18-09; €: Mandatory field in Stoffenmanager Nano entries

hypothesis applied is that the biological effects of highly water-soluble NM will not differ significantly from that of coarser particles. In Stoffenmanager Nano and NanoSafer low solubility (<0.1 g/L and <1 g/L respectively) is a prerequisite for applying the tool. The IVAM Guidance also use <0.1 g/L as the limit between low and high solubility. In the ANSES tool, low solubility rate (slower dissolution than 1 h) is a discriminating factor moving the hazard level one band up. In the CB Nanotool solubility is referred to with no further detail, whereas the Precautionary Matrix considers the half-life of the NM in the body. Noteworthy, the type of solubility information asked for in the ANSES tool and the Swiss Precautionary Matrix is not available in standard technical data- or safety data-sheets. It is also notable that the definition by which the solubility is defined in the different tools has great influence on which materials that will be included or not for CB assessment.

Only two tools, the Precautionary Matrix and NanoSafer, request information on whether the NM have been chemically coated/

Table 3
Physicochemical properties and material characterization required by the CB tools.

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Physicochemical properties and material characterization						
Stability (half-life) of the primary particles present in the nanomaterial under environmental conditions			H			
Length: diameter of the fiber (aspect ratio) (If you selected 'No' in the option 'Does the product contain fibers/fiber like particles?') (*Choose from selection*: Unknown/unknown; Unknown/known; Aspect ratio >= 3:1; Aspect ratio < 3:1; >= 5000nm/unknown; < 5000nm/unknown)[€]				H		
Moisture content (*Choose from selection*: Dry product (<5% moisture content); 5 – 10% moisture content; > 10% moisture content)[€] [if source domain: Handling of bulk aggregated/agglomerated nanopowders]				E		
Moisture content (*Choose from selection*: Dry product (<5% moisture content); 5 – 10% moisture content; > 10% moisture content)[€] [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [if Product type: Intermediate][if Product appearance: Granules/flakes]				E		
Viscosity of the liquid[€] (*Choose from selection*: Liquid with low viscosity (like water); Liquid with medium viscosity (like oil); Liquid with high viscosity (like paste, syrup)) [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [if Product appearance: Particles dispersed in a liquid]				E		
Is the nanomaterial a biopersistent fibre? (Yes/No)					XH	
Substance dissolution time > 1h (Solubility)					H	
Evidence that reactivity is not higher than bulk/analogous material?					H	
Dimensions of the primary nano-object: Shortest dimension (nm); The middle dimension (nm); longest dimension (nm).						NH
Is the material surface modified (coated / functionalized) ?						H
What is the material's specific density? (g/cm^3)						NE
What is the solubility of the material ? (g/L)						NH
What is the material specific surface area (powder material) ? (m^2/g)						NE
Physi cochemical properties and material characterization						
Chemical form (e.g., liquid suspension, dry powder, etc.)[£]	–					
Particle diameter (nm)[£]	H					
Particle shape[£]	H					
Surface reactivity[£]	H					
Solubility[£]	H					
Aggregation or agglomeration potential[£]	–					
Purity of material[£]	–					
Flammability[£]	–					
Flash point[£]	–					
Size distribution of the primary particles in the material or product (in nm)		–				
Does the material or product involve fibrous particles (yes/no; if yes, specify its length and diameter)		H				
Water solubility (the substance is soluble in water when its solubility is higher than 100 mg/l)		H				
Density (in kg/dm^3)		–				
Material containing primary particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the primary particles in the number size distribution, one or more external dimensions is in the size range 1 nm -100 nm or (Ii the number size distribution is unknown)			N			
Material where the specific surface area by volume is greater than 60 m^2/cm^3			N			
Size of the primary particles in the materials (free, bound, aggregated or agglomerated)			N			
Are coated / functionalised nanomaterials involved?			–			
Redox activity of the nanomaterial			H			
Catalytic activity of the nanomaterial			H			
Oxygen radical formation potential of the nanomaterial			H			
Induction potential for inflammatory reactions of the nanomaterial			H			
Stability (half-life) of the primary particles present in the nanomaterial in the body			H			

N: Nano relevance; H: Hazard scaling; E: Exposure scaling; I: Available Info/Uncertainty; X: decision tree preliminary questions; –: input not used for the assessment. £: Nanomaterial Field-Information Form for CB Nanotool €: Mandatory field in Stoffenmanager Nano entries

functionalized. The information appears only to be directly applied in NanoSafer for hazard band allocation. However, the Swiss Precautionary Matrix instructs to make a separate (additional) matrix for the modified particle in case the coating is not stable. On the other hand, only the CB Nanotool and the Precautionary matrix ask for information on the agglomeration and aggregation behavior of the NM.

Interestingly, the physico-chemical properties and material characterization data are used in different ways in the different tools. In

Table 4
Toxicology data.

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Toxicology data						
Toxicity (lowest OEL) of parent material[£]	H					
LD50 of parent material[£]	–					
Mutagenicity of parent material[£]	H					
Carcinogenicity of parent material[£]	H					
Reproductive toxicology of parent material[£]	H					
Dermal toxicity of parent material[£]	H					
Asthmagen of parent material[£]	H					
Substrate toxicity[£]	–					
LD50[£]	–					
Mutagenicity of nanoscale material[£]	H					
Carcinogencity of nanoscale material[£]	H					
Reproductive toxicology of nanoscale material[£]	H					
Dermal toxicity of nanoscale material[£]	H					
Asthmagen of nanoscale material[£]	H					
Effects on organisms[£]	–					
Bioaccumulation potential[£]	–					
Biopersistence/degradation[£]	–					
Has the mother material been classified as CMR substance? (Carcinogenic, Mutagenic, Reproduction toxic)		–				
Do the nanomaterials form agglomerates >500nm?			N			
Does de-agglomeration of agglomerates (or aggregates) to primary nanoparticles or agglomerates <500nm occur under physiological conditions?			N			
If agglomerates between 500nm and 10μm are present, can employees or consumers take these in via the lungs?			N			
Toxicology data						
Inhalation hazard[€] (If you selected 'No' in the option 'Does the product contain fibers/fiber like particles?' Choose from selection: Unknown; Mutagenic (and possibly carcinogenic) and/or sensitizing; Carcinogenic (not mutagenic), reprotoxic and/or very toxic; Toxic, corrosive and/or respirator allergens; Harmful and/or irritating; Non hazardous)				H		
Is there a preliminary hazard band of the bulk material or most toxic analogus?					H	
What is the material's OEL? (mg/m^3)						H
Risk (R-Phrases: General toxicity (R20-R28; R33; R36-39; R41; R48; R65; R68); Carcinogenic effect (R40; R45;R46; R49); Reprotoxicity(R60-R64); Allergy and sensitization(R42-R43); Neurotoxicity (R67))						H

N: Nano relevance; H: Hazard scaling; E: Exposure scaling; I: Available Info/Uncertainty; X: decision tree preliminary questions; –: input not used for the assessment. £: Nanomaterial Field-Information Form for CB Nanotool €: Mandatory field in Stoffenmanager Nano entries

most of the tools the data are used for hazard band allocation alone, but in some cases they are also used for nanomaterial identification. In NanoSafer physico-chemical data (specific surface area and specific gravity) are also used for scaling of the final risk level. It is also interesting to note that the Stoffenmanager Nano and the ANSES tool use relatively few physico-chemical input data, whereas a larger suite of data are requested and used by the CB Nanotool, the Precautionary Matrix and NanoSafer.

3.2.3. Toxicological data

It is observed that different approaches are used for hazard ranking in the different tools and with substantial differences in the level of detail. Table 4 lists the *Toxicological data* requested by the different tools and by the number of inputs this type of information (in combination with physicochemical properties) is of high importance for the hazard band allocation in the CB Nanotool, Stoffenmanager Nano and NanoSafer. The IVAM Guidance and the Precautionary Matrix base their hazard assessment on the physicochemical properties and material characterization alone. In the ANSES and NanoSafer tools, the hazard band allocation is determined from a combination of material characteristics and known hazards of the bulk material.

The CB Nanotool especially asks for the mutagenicity, carcinogenicity, reproductive toxicology, dermal effects, asthmagenicity of both the nanomaterial and the parent material; and the OEL of the parent material. Default entries are available if answers are unknown.

Stoffenmanager Nano asks one specific question on whether the nanomaterial has been associated with an inhalation hazard to be selected from 6 possibilities covering non-hazardous to carcinogenic effects in a drop-down menu (Table 4). However, the tool also asks whether the assessment concerns any of the nanomaterials included in the test program under the OECD Working Party on Manufactured Nanomaterials (OECD, 2015). It was not evident, from our analysis, if selection of any of these materials will provide additional default hazard data for the assessment.

NanoSafer asks the user to tick relevant risk phrases known for the nearest analog bulk material among at least 30 pre-selected inhalation-relevant risk phrases covering: general toxicity, carcinogenicity, reprotoxicity, allergy and sensitization, and neurotoxicity. The user is also requested to enter the OEL of the nearest analog bulk material. The hazard band allocation is based on these data combined with scores for the physico-chemical properties (coating and aspect ratio) of the NM.

Interestingly, all the tools refer to the bulk parent material when information on the nanomaterial is not available and they generally agree that material information should be gathered from technical and safety data sheets. This highlights the need for ensuring high standards of these documents.

Table 5
Requested information for "Exposure Characterization" and "Characterization of Control measure".

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Exposure Characterization						
Handling description[£]	–					
Dustiness/mistiness[£]	E					
Average daily amount used[£]	–					
Estimated maximum amount of chemical used in one day (mg)[£]	E					
Frequency of operation[£]	E					
Duration of operation[£]	E					
Route(s) of exposure[£]	–					
Number of employees with similar exposure[£]	E					
Primary production nano-material		–				
Secondary production nano-product		–				
Professional use nano-product		–				
Reception and storage of nanomaterials/-products van nanomaterialen		–				
Opening of the packaging		–				
Addition of the nanomaterial		–				
Production of the nanomaterial		–				
Working with NMP		–				
Sampling (quality control)		–				
Filling / packaging of end product		–				
Transfer and transportation		–				
Waste treatment and removal of waste		–				
Other		–				
Used amount (in kg, liter)		–				
Emission of dust/mist/haze possible (yes/no)		E				
Duration of the activity (in minutes)		–				
Frequency of the activity (times per day, week or month)		–				
Amount of workers exposed (N)		–				
Air, Aerosols <10 μm			E			
Air, Aerosols >10 μm			E			

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Exposure Characterization						
Liquid media			E			
Solid matrix, not stable under relevant process conditions or conditions of use			E			
Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial mobile			E			
Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial not mobile			E			
Dustiness[€] (Choose from selection: Medium (50-150mg/kg); Very high (>500 mg/kg); High (>150-500 mg/kg); Unknown)[if source domain: Release of primary particles during actual synthesis or Handling of bulk aggregated/agglomerated nanopowders]				E		
Dustiness[€] (*Choose from selection*: Granules/flakes; Firm/granules or flakes)[if source domain: Spraying or dispersion of ready-to-use nanoproduct and Product appearance: Granules/flakes]				E		
Characterize your task[€] (*Choose from selection*: Flame Pyrolysis; Mechanical Reduction (Machining); Chemical Vapor Condensation; Wet Chemistry (Functionalization); Wet Chemistry (Synthesis – into solution); Sintering; Mechanical Reduction (Preparation for Imaging); Wet Chemistry (Synthesis – with solution)[if source domain: Release of primary particles during actual synthesis]				E		
Characterize your task[€] (*Choose from selection*: Handling of products, where due to high pressure, speed or foce large quantities of dust are generated and dispersed; Handling of products, with a relatively high speed/foce which leads to disperions of dust; Handling of produtcts with low speed or little force or in medium quantities (several Kilograms); Handling of product in small amounts (up to 100 gram) or in situation where only low quantities or products are likely to be released; Handlign of products in closed containes; Handling of products with medium speed of force, whichleads to some dispersion of dust; Handling of products with low speed or little force, which leads to some dispersion of dust) [if source domain: Handling of bulk aggregated/agglomerated nanopowders] or [if source domain: Spraying or dispersion of ready-to-use nanoproduct and if Product type: Intermediate and Product appearance: Granules/flakes]				E		

(continued on next page)

Table 5 (*continued*)

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Exposure Characterization						
Characterize your task € (*Choose from selection*: Handling of liquids at high pressure resulting in substantial generation of visible mist or spray/haze; Handling of liquids on large surface or large workpiece; Handling of liquids using low pressure, low speed with large or medium quantities; Handling of (almost) undisturbed liquids (very low speed), very small quantities (under controlled conditions) of liquids in tightly closed containers)[if source domain: Spraying or dispersion of ready-to-use nanoproduct] [if Product type: Ready-to-use-product]				E		
Characterize your task € (Choose from selection: Handling of liquids at high pressure resulting in substantial generation of visible mist or spray/haze; Handling of liquids on large surface or large workpiece; Handling of liquids using low pressure, low speed with large or medium quantities; Handling of (almost) undisturbed liquids (very low speed), very small quantities (under controlled conditions) of liquids in tightly closed containers) [if source domain: Spraying or dispersion of ready-to-use nanoproduct] [if Product type: Intermediate] [if Product appearance: Particles dispersed in a liquid]				E		
Number of exposed employees (n)				–		
Production or usage volume in kg a year				–		
Start date of period worked with the product				–		
End date of period worked with the product				–		
Last update date of additional registration				–		
Duration task (4 to 8 hours a day; 2 to 4 hours a day; 0,5 to 2 hours a day; 1 to 30 minutes a day) €				E		
Frequency task (4 to 5 days a week; 2 to 3 days a week; Approximately 1 day a week; Approximately 1 day per 2 weeks; Approximately 1 day a month; Approximately 1 day a year) €				E		

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Exposure Characterization						
Is the task being carried out in the breathing zone of an employee (distance head-product < 1 meter)? (Yes/No) € (Please note: that if your choice for 'yes - the task is being carried out in the breathing zone' then the option 'the employee does not work in a cabin' is automatically selected. If however you do want to select a cabin, then return to 'is the task being carried out in the breathing zone' and select 'no')				X		
Is there more than one employee carrying out the same task simultaneously € (Yes/No) (If you selected 'Yes' in the option 'the task is being carried out in the breathing zone')				–		
Volume of the working room (Volume < 100 m3; Volume 100 -1000 m3; Volume > 1000m3; Work performed outside) €				E		
Ventilation of the working room (No general ventilation; Mechanical and or natural ventilation; Spraying booth) €				E		
Specific cases of band modification due to process operation: Dust generated by external forces; Melting; Dispersion in liquid; Powder generated by evaporation (dustiness of the powder)/ Spraying; Spraying.					E	
Specific cases of band modification due to the natural tendency of the material or the matrix: Friable solid; Highly volatile liquid; High or moderate dustiness powder.					E	
The physical form of the nanomaterial (Solid: solid materials containing nanomaterials or having a surface that is nanostructured or covered with nanoparticles. Liquid: suspension of free nanoobjects and/or aregates/agglomerates of nano-objects smaller than 100nm in a liquidmedium, regardless of its viscosity. Powder: mass of nanomaterials (free nanoobjects and/or aggregates/agglomerates of nano-objects smaller than 100 nm). Aerosol: liquid or solid suspension of nanomaterials (free nano-objects and/or aggregates/agglomerates of nano-objects smaller than 100 nm) in a gas (including air)), whether raw or included in a matrix and					E	

Table 5 (*continued*)

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Exposure Characterization						
Name the work situation or process to be modeled						–
Select the type of process (Powder Handling; Fugitive Emissions)						–
What is the dustiness index for respirable dust (Enter data or select dustiness level if data is not available) mg/Kg (Very Low (0-10) Low (10-50) Moderate (50-250) High (> 250)) (mg/Kg) [Powder handling]						E
Emission rate of respirable dust (mg/min) [Fugitive emissions]						E
Activity handling energy factor (dimensionless)						E
Total mass of material handled in each work cycle (kg)						E
Duration of work cycle (min)						E
Pause between work cycles (min)						E
Number of work cycles per day (n)						E
Amount of nanomaterial handled in each transfer (spoon, bag, big-bag etc) (kg)						E
Time required for each transfer (spoon, bag, big-bag etc) (min)						E
Volume of the work room: Length (m), Width (m), Height between floor and ceiling (m)						E
Air-exchange rate (h-1)						E
Characterization of Control measure						
Engineering controls£	–					
Administrative controls£	–					
List of PPE used£	–					
Cleanup procedures for spills or releases£	–					
Disposal procedures (e.g., hazardous waste?)£	–					
Container type used for storing materials£	–					
Equipment to be used with nanomaterials£	–					
Location of spill mitigation equipment, engineering control equipment, safety equipment (e.g. eyewash, safety showers)£	–					
Cleaning and maintenance		–				

Entry	CB Nanotool	IVAM Guidance	Precautionary Matrix	Stoffenmanager Nano	ANSES	NanoSafer
Characterization of Control measure						
Is the working room being cleaned daily? (Yes/No)€				E		
Are the inspections and maintenance of machineries/ancillary equipment being done at least monthly to ensure good condition and proper functioning and performance? (Yes/No)€				E		
Local control measures (No control measure at the source; Use of product that limits the emission; Local exhaust ventilation; Containment of the source; Containment of the source with local exhaust ventilation; Glove boxes/bags)€				E		
Is the employee situated in a cabin? (The worker does not work in a cabin; The worker works in a cabin without specific ventilation system; The worker works in a separated (control) room with independent clean air supply)€				E		
Is personal protective equipment applied? (None/Filter mask P2 (FFP2)/Filter mask P3 (FFP3)/Half mask respirator with filter, type P2L/Half mask respirator with filter, type P3L/Full face respirator with filter, type P2L/Full face respirator with filter, type P3L Half/full face powered air respirator TMP1 (particulate cartridge)/Half/full face powered air respirator TMP2 (particulate cartridge)/Half/full face powered air respirator TMP3 (particulate cartridge)/Full face powered air respirator TMP3 (particulate cartridge)/Hood or helmet with supplied air system TH1/Hood or helmet with supplied air system TH2/Hood or helmet with supplied air system TH3)€				E		

N: Nano relevance; H: Hazard scaling; E: Exposure scaling; I: Available Info/Uncertainty; X: decision tree preliminary questions; –: input not used for the assessment. £: Nanomaterial Field-Information Form for CB Nanotool; €: Mandatory field in Stoffenmanager Nano entries.

3.2.4. Exposure characterization

The results in Table 5 show that the tools also vary considerably in their number of input parameters required to complete the *Exposure Characterization* and to what extent the information is used in the exposure band allocation. For example, the IVAM Guidance tool asks 18 questions, but in the end only uses 1 parameter for allocation of the exposure band. This is due to the fact that IVAM guidance request information to form the basis for a dialog and qualitative assessments. At the other end Stoffenmanager Nano and NanoSafer asks for 22 and 13 questions and use 15 and 11 respectively for allocation of the exposure band. The major differences between Stoffenmanager Nano and NanoSafer is the calculation procedures and differences in the output where "risk time" (assessment considering the duration and frequency of exposure) and "risk task" (assessment considering the specific task alone) are assessed in Stoffenmanager Nano, whereas, the acute and chronic (daily) exposure is assessed by NanoSafer. Another difference is that risk management measures can be contemplated in Stoffenmanager Nano but not in the NanoSafer 1.0 model where the exposure controls are recommended based on the assessment. Inclusion of risk management measures are considered in current further developments of the NanoSafer model.

Almost all the tools ask for the amount of material handled during each task, but the questions address different aspects. For instance, the CB Nanotool asks for "maximum daily amount used" whereas Stoffenmanager Nano asks for "production or usage volume in kg a year" and NanoSafer asks for "total mass of material handled

Table 6
Summary of input parameters used by the CB-tools for determine the exposure assessment.

Tool entries-input parameter	IVAM Guidance	ANSES	Precautionary Matrix	CB Nanotool	NanoSafer	Stoffenmanager Nano	ECHA R. 14	STR
Physicochemical properties and material characterization								
Physical state	X	X	X	X	X	X	+	S
Dustiness		X		X	X	X	+	S
Moisture						X		S
Exposure Characterization-contextual information process related								
Work process description		X			X	X	+	S
Amount			X	X	X	X	+	S
Duration				X	X	X	+	S
Frequency			X	X	X	X		S
Emission of dust/mist/haze possible	X							S
Pause between work cycles					X			S
Time required for each transfer					X			S
Activity handling energy factor					X			S
Emission rate of respirable dust					X			S
Exposure Characterization-contextual information work place related								
Number of employees with similar exposure				X				
Air-exchange rate					X	X		T
Volume of the work room					X	X		T
Inspections and maintenance of machineries						X		T
Cleaning the working room						X		T
Location: near field/far field)						X		T
Characterization of Control measure								
Local control measures						X	+	T
Personal enclosure						X		T
Personal protective equipment						X		R

X: parameters used by the CB-tools; +: input parameters required by ECHA technical guidance R.14; S: Source; T: Transmission; R: Receptor; in compliance with STRmodel.

in each work cycle". A number of tools such as the CB Nanotool, Stoffenmanager Nano and NanoSafer also consider the duration and frequency of the operations. Such differences demonstrate the different types and levels of assessments made.

Finally, the ANSES tool requests data on the physical form of the nanomaterial matrix and specific material transformations for different physical forms during the operational tasks, whereas *Substance emission potential* and *Activity emission potential* are requested data in Stoffenmanager Nano and in NanoSafer (given substance emission rate or calculated from dustiness indexes and activity energy factors).

3.2.5. Characterization of control measures

The elements included under the *Characterization of control measures* are summarized in Table 5. The CB Nanotool and Stoffenmanager Nano ask several questions on this topic whereas the IVAM Guidance only asks one question in the topic. However, none of the 8 input parameters asked in the CB Nanotool are used for quantification. Interestingly, the parameters in this category also includes other contextual information, including the cleanliness of the work area and the number of employees potentially exposed and their behavior when handling the nanomaterials, than just the efficacy of the engineered and personal protection equipment. Stoffenmanager Nano is the only tool that currently takes into account characterization of the control measures for the calculation of the exposure scaling. This is by assuming that the efficiencies of exposure control measures have similar performance to nanomaterials as to conventional dust emissions (Fransman et al., 2008).

3.3. Banding allocation and scaling principle

Table 1 demonstrated that the different CB tools differed in regard to the number of hazard and exposure bands and in how they are combined. As demonstrated in Tables 2–6, the hazard and exposure bands are also to some extent allocated using different parameters or specific forms of the input parameter and at different levels of detail. In addition the scales and classification of the hazard and exposure bands vary between the different tools.

In the CB Nanotool, the hazard and exposure banding is based on the sum of all points allocated for each of the 20 parameters, 15 for hazard (severity) and 5 for exposure (probability). The exposure band is divided into four bands with the ranges: 0–25 = extremely unlikely, 26–50 = less likely, 51–75 = likely, 76–100 = probable. In the case of the Hazard band allocation, the user is asked to evaluate their nanoparticle using up to 15 parameters. For instance, surface chemistry must be ranked high, medium, low or unknown giving it a value of 10, 5, 0 and 7.5, respectively. Similarly, particle shape must be evaluated in regard to whether it is a) Tubular or fibrous, b) Anisotropic, c) Compact/spherical, and d) Unknown corresponding to value of 10, 5, 0 and 7.5, respectively. The hazard band is defined from the sum of all the values assigned.

The IVAM Guidance identifies three hazard categories for nanomaterials and nanoproducts ranging 1, 2, and 3; the higher the category number, the higher the anticipated health risk. The lowest category 1 is relatively harmless and given to water-soluble nanoparticles; intermediate category 2 and highest category 3 are allocated to synthetic, persistent (non-fibrous) nanomaterials and fibrous, non-soluble nanomaterials respectively. The three exposure categories ranging from the lowest; allocated for the case of no emission of free nanoparticles due to working in full containment; over an intermediate category; allocated for the case when emission of nanomaterials embedded in a matrix is possible; to finally the highest category; allocated to the case when emission of free nanomaterials is possible.

Stoffenmanager Nano and the ANSES tool have a similar approach for the hazard allocation. It consists of stepwise binary decisions that allocate the band according to the answer to the input parameters. In Stoffenmanager Nano, for instance, as a first step, asks whether the water solubility is lower than 0.1 g/L and then if it is a persistent fiber. If both of these entries are positive, this will automatically result in an allocation in the highest band. If it is not a persistent fiber, the specific hazard data is taken into consideration for the banding allocation. The allocation of control bands in ANSES is based on some preliminary question such as: does the product contain nanomaterials; has the nanoproduct already been studied with regard to regulations on classification and labeling; is it a biopersistent fiber; and afterwards allocates the bands according to the e-COSHH Essentials tool (COSHH, 2002). The nanomaterial hazard band can be increased above the e-COSSH Essentials band of the corresponding bulk material, depending on its solubility or its reactivity.

The exposure band allocation in Stoffenmanager Nano is based on the principles in the source-to-receptor model described in Schneider et al. (2011), evaluating different parameters (background concentration, near-field and far-field source concentrations, a multiplier for the reduction of exposure due to control measures at the worker or due to use of personal protective equipment, multiplier for duration and frequency of the handling). The exposure band is based on a score with four value ranges (<0.002; 0.002–0.2; 0.2–20; >20).

The emission potential levels in the ANSES tool is determined following a completely different approach allocating the potential emission according to the physical form of the nanomaterial matrix, whether Solid, Liquid, Powder or Aerosol, entering the process at the workplace; and specific material transformations due to the natural tendency of the material/matrix or due to process operation for different physical forms. The lowest band is allocated for the "Solid physical" form, the second band for the "Liquid form", the third for "Powder form" and the fourth highest for "Aerosol".

In NanoSafer the hazard assessment is based on a combination of binary grouping principles and quantifications based on toxicological rules, physicochemical properties and hazard properties of analog bulk materials. NanoSafer allocates four bands for the hazard (HCB1 = [0.00;0.25], HCB2 =]0.25;0.50], HCB3 =]0.50;0.75], and HCB4 =]0.75;1.00]), with ranking value from 0.2 to 1, where 1 is the maximum value given to materials estimated to be highly hazardous. The value 0.2 is given for materials with OEL's above 1 mg/m^3 and no further reported physico-chemical properties of risk and risk sentences relevant for the airways. In NanoSafer the hazard evaluation of the nanomaterial is based on the existing knowledge on toxicological effects for the nearest analog bulk materials and on specific physical–chemical data information of the NM assessed. This includes the morphology of the primary nanomaterial, chemical surface modification, the OEL for the nearest analog bulk material, and risk or safety phrases for the nearest analog bulk material. Low solubility (<1 g/l) of NM is a criterion for making a hazard band allocation in NanoSafer. The final hazard band is calculated by combining the individual hazard contributions through a score assigned to each contribution for the aspect ratio, surface modification, OEL and specific risk or safety phrases.

The NanoSafer exposure evaluation can be made based on user-defined scenarios and the method, as in Stoffenmanager Nano, follows the conceptual model for assessment of inhalation exposure developed by Schneider et al. (2011). Allocation of the exposure bands takes into account: the respirable rotating drum dustiness index; the activity handling energy factor; the total mass of material handled in each work cycle; the duration of work cycle; the pause between work cycles; the number of work cycles per day; the amount of nanomaterial handled in each transfer (spoon, bag, big-bag etc.); the time required for each transfer (spoon, bag, big-bag etc.); the volume of the work room; and the air-exchange rate. An alternative approach considering constant (point source or fugitive) emission rates instead of dustiness for powder processes is also possible. The control bands (risk levels) is a combination of the derived hazard and exposure bands in a two-dimensional decision matrix, ranking from the lowest RL1 to highest RL5 associated with general recommendations for risk management. However, the procedure in NanoSafer is different from that in the other control banding tools as the final risk level is an integrated assessment considering the hazard band and exposure scaling derived from the calculated exposure potential, the specific surface area of the powder, the specific gravity, and the OEL for the nearest analog bulk material.

As previously mentioned, the Swiss Precautionary Matrix differs from the other tools since it is not aimed at a band allocation but only at determining whether there is a need for action (classified as B at scores >20) or not (classified as A at scores 0–20).

3.4. The control band outcome

The CB tools also differ in the number of final control bands and in how they integrate the hazard- and exposure bands in order to provide the overall assessment. The control band allocation consist of 4 bands for the CB Nanotool, the IVAM Guidance and Stoffenmanager Nano, called: risk level, control level and priority band, respectively. The ANSES tool and NanoSafer both have 5 control bands called: control level and risk level, respectively. As mentioned above the Precautionary Matrix has only two classifications, A: low need for action and B: nanospecific action is needed.

Besides differing in regard to how they combine the hazard band and the exposure band into a control band, there is, also differences in the typology used to report the result from the assessment and recommendations. In the CB Nanotool, ANSES tool, IVAM Guidance, and NanoSafer the outcome consists of a control-banding risk level which is associated with a general risk management recommendation on the level of engineered and personal exposure control that should be applied. NanoSafer also provides e-learning on good practice and inspiration for exposure reduction. Finally, the Stoffenmanager Nano control-banding output consists of a ranking priority of action needed.

The differences in the final output and the relative scaling, on top of different information requirements, mean that it is not straight forward to compare results from the different tools in a "quantitative" comparative study.

3.5. Determinant exposure evaluation parameters

The exposure determinants should be interpreted as all the parameters that are de facto used in the models to estimate or rank exposure. Identification of a set of exposure determinants does not necessarily mean that they are all main factors for the exposure evaluation since the analysis does not include a sensitivity analysis of the models. The results are held up against input parameters defined in ECHA Guidance R.14 and the conceptual source-to-receptor model by Schneider et al. (2011), where the input parameters are sorted according to their use in the source (S), dust transmission (T), and receptor (R) parts of the model. The source component includes activity emission potential and substance emission potential. The transmission component considers the modifying factors of localized control, segregation, dilution, personal behavior, separation, and surface contamination. The receptor component includes only the use of respiratory protective equipment (ISO/TS 27687, 2008). The general result of the analysis is summarized in Table 6. The rows presents the input parameters grouped in accordance with ISO/TS 12901-2:2014 (ISO/TS 27687, 2008). It is evident that the majority of the input parameters are in the domain for estimation of exposure at the source. The Stoffenmanager Nano and NanoSafer both consider parameters for the transmission and only Stoffenmanager Nano currently considers the respiratory protection equipment (RPE). When compared to the ECHA Guidance R.14 on Occupational exposure estimation, it should be noted that RPE, as well as several other parameters in both the source and transmission domains, are not core information requirements for Tier 1 exposure scenarios.

Some tools (i.e. IVAM Guidance, ANSES) base the exposure assessment on a limited number of parameters, mainly focusing on the physicochemical properties and material characterization, which then can be referred to as the source component of the Source Transmission Receptor (STR) model. Stoffenmanager Nano and NanoSafer estimate the exposure on more parameters and also include contextual information related to process and workplace and characterization of control measures (Stoffenmanager Nano) for a more elaborate assessment of work scenario more in line with the STR model.

The IVAM Guidance and the ANSES tools only use the input on physical state of the nanomaterial for the exposure assessment. This parameter is also part of the core information requirement for Tier 1 exposure scenarios listed in the ECHA Guidance R.14 on occupational exposure estimation. Notably, the IVAM Guidance bases the final evaluation on the user's judgment only telling whether or not emission is possible without specifying any exposure level of it. In addition to this, the ANSES tool includes also specific material transformations of the physical state to take into account the tendency of certain materials to change from one physical form to another due to the material/product characteristics e.g. friable solid, highly volatile liquid; or due to process operation e.g., powder generated by evaporation, dispersion in a liquid.

In the Precautionary Matrix it is also the physical state of the material, which is used to scale the potential for exposure, but the scaling is further refined considering the amount of material used and the frequency with which a worker handles the nanomaterial. Therefore, the Precautionary Matrix input parameters comply with the source component of the STR model.

As observed, the amount of NM handled and the frequency of handling are determinant parameters in several models. However, the terms are not requested and used in the same forms. In the Precautionary Matrix and the CB Nanotool, the amount used refers to the amount used in one day. Stoffenmanager Nano considers the amount as the exact weight percentage in the material, intermediate, spray or end-product. In NanoSafer, the exposure assessment is based on the total amount used in the process (work cycle) as well as the amount used per task in the work cycle. This, coupled with information on duration, volume of work-room and air-exchange rates allows NanoSafer to estimate and subsequently rank the acute (15 min average) and chronic (8-h daily) exposure potential. In Stoffenmanager Nano the long term exposure potential is assessed by taking the long-term frequency of use into account (van Duuren-Stuurman et al., 2012). The frequency input parameter in Stoffenmanager Nano can vary from 4 or 5 days per week to 1 day per year, which will then be determinant for the long or short term exposure estimation. In the CB Nanotool, the frequency parameter is used in the same way as in Stoffenmanager Nano, (e.g. daily, monthly frequency), while in NanoSafer the frequency parameters accounts for the number of work cycles per day. In spite of its clear importance to understanding the exposure, frequency is not considered a core information requirement for Tier 1 exposure scenarios in the ECHA Guidance R.14 on occupational exposure estimation.

When it comes to the parameters related to the work-place it is noteworthy that room size and ventilation rate are only taken into account as determinant parameters in Stoffenmanager Nano and NanoSafer. The room size and the ventilation rate are important factors that control the dilution of the contaminants in the room, considered also as a modifying factor in the STR model. Room size is also a parameter considered in Tier 1 REACH tools.

In contrast to the other tools Stoffenmanager Nano considers also other work-place related parameters as it accounts for two input parameters for determining the background source, by asking whether the machineries are well maintained and whether the work place is being cleaned daily. These parameters, in combination with the intrinsic emission, are determinants for calculating the background concentration; and a parameter accounting for the local control measure, which is a determinant multiplier to calculate the potential exposure.

Control measures are only considered in Stoffenmanager Nano. Two different parameters can be selected for the engineering control and one parameter for the use of personal protection equipment. All are determinant multipliers for calculating the potential exposure and can be used in the assessment upon choice. Inclusion of control measures is in compliance to the receptor component of the STR model but is not a core information requirement for Tier 1 exposure scenarios in the ECHA Guidance R.14. In fact the ECHA guidance suggests generally not to consider personal protection equipment, but local exhaust ventilation for the first exposure estimation.

4. Discussion

When comparing existing tools and frameworks it is important to note that such a comparative analysis can never do full justice. The tools presented here are all helpful in the primary evaluation of the potential exposures and risks related to production and application of nanomaterials although they do not meet the intentions set out in ECHA Guidance R.14 (ECHA, 2012a). However, these tools can in principle all serve the Tier 1 purpose in R.14 due to the fact that their output is qualitative and follow various rankings or control banding approaches. It is furthermore stated for all of the CB-like tools that they are to be applied in early precautionary risk assessment. This is when no risk assessments can be performed based on toxicological and exposure evidence. Hence, many of the tools, examined in this paper, are in principle potential candidates for fulfilling the Tier 1 requirements set out in REACH and specified in ECHA Guidance R.14 (ECHA, 2012a).

When it comes to comparison with REACH requirements and compliance with the STR model, a number of key aspects should be taken into consideration:

First of all, it should be taken into account that the aim of a CB-tool in general is not to be a quantitative model, which is the aim of the STR model. The CB Nanotool, Precautionary Matrix, Stoffenmanager Nano, ANSES and NanoSafer were developed in order to help developers, producers and users of NM to complete first precautionary risk estimations and apply precautionary exposure control. Some were developed more with the aim to enable precautionary screening assessments to determine whether there is a need for a subsequent assessment in depth (Precautionary Matrix). Others were developed with the aim to protect researchers in work at laboratory scale (CB Nanotool), or to provide guidance for organization of safe work with nanomaterials (IVAM Guidance) or with the aim to perform simple precautionary risk assessments without taking the contextual information at the work place into account (ANSES). Although varying greatly in focus and scope, most of the tools give guidance on how to make this first-hand assessment of the hazards and exposure associated with NM and their use(s), respectively.

Second, several of the existing exposure estimation tools listed in R.14 (ECHA, 2012a) require a substantial number of input parameters and so do many of the CB nanotools. Some of the CB nanotools even ask for input parameters that are not standard information in technical and safety data sheets and not even readily available in the scientific literature (e.g. surface reactivity and degree of agglomeration). In more recent developments, test guidance to obtain this data is slowly emerging (Höck et al., 2013; Studer et al., 2013).

Third, as existing exposure limits are given for conventional compounds, the tools listed in R.14 (ECHA, 2012b) specifically focus on exposure estimation and most of them focus on inhalation. Only a few are applicable for dermal exposure assessment. Most of the CB nanotools also focus on inhalation risk only and use an estimate of the likelihood of exposure or a more-or-less precise relative scale. In CB-tools, built-in hazard assessment or scaling models are necessary to enable an overall risk assessment, when the hazard is not known.

Overall, it seems that, among all the CB tools analyzed, Stoffenmanager Nano and NanoSafer have the closest resemblance with the conceptual exposure assessment model by Schneider et al. (2011) and the core information requirements of the ECHA Guidance R.14 (Table 6). Regarding the input parameters, Stoffenmanager Nano and NanoSafer are somewhere in between the ECHA Guidance R.14 Tier 1 and higher Tier requirements including the aerosol-dynamic STR-like (Source-Transmission-Receptor) modeling. However, the relative importance of the different additional input parameters considered in the STR model as compared to simpler models is not known and should be further investigated in future work.

From Table 6, it can be noted that the descriptive parameters in the work process are mainly taken into account by Stoffenmanager Nano and NanoSafer and are in agreement with the determinant parameters in ECHA Guidance R.14 and the STR model. Moreover as suggested by Kuhlbusch et al. (2011) this information is also needed for a "systematic approach of harmonization and standardization" because for a better exposure evaluation it is necessary to differentiate the various work scenarios.

Stoffenmanager Nano and NanoSafer use more parameters for complying with the source-to-receptor model than any of the other CB tools: 7 determinant parameters for the source component (in Stoffenmanager Nano) and 10 determinant parameters for the source component (in NanoSafer) as well as 7 and 2 determinant parameters for the transmission component in Stoffenmanager Nano and NanoSafer, respectively. The same is the case when it comes to the compliance with the core information requirement of the ECHA Guidance R.14, for which 6 and 5 determinant parameters are used in Stoffenmanager Nano and NanoSafer, respectively.

It is evident from Table 6 how the number of input parameters varied from the simplest to the more complex models. Only one parameter is required in the ANSES tool to scale exposure while fifteen input parameters are requested in Stoffenmanager Nano. The simplest tools regarding input requirements are the ANSES and the IVAM tools while NanoSafer and Stoffenmanager Nano are the most complex tools requesting and using a much higher number of input parameters. One key issue of using ECHA exposure assessment tools is that they assume the presence of OEL, but only in rare cases we have OELs for nanomaterials and the first recommendations have just emerged. Therefore, for evaluating the risk level associated with production or work with a NM in the work-place, a certain number of input parameters are especially needed to enable hazard estimates when data and OEL does not exist. These parameters are clearly control banding requirements and not (only) exposure assessment requirements.

From a user perspective, it would be desirable to use a tool with a low number of input parameters (e.g., the ANSES tool or the IVAM Guidance) to complete an exposure assessment. However a more advanced tool with a higher number of input parameters is likely to have a higher dynamic range while still enabling a balance between ensuring a safe work environment and "being able to work". For instance looking at Table 6 and comparing the number of input parameters required by the IVAM Guidance and NanoSafer, respectively, it is evident that the IVAM Guidance is very precautionary dividing the scenarios into cases with exposure or not while NanoSafer evaluates the level of potential exposure. In this respect Stoffenmanager Nano and NanoSafer are more advanced in terms of developing a tool for use in accordance with R.14 and for providing a quantitative model for estimation of the occupational exposure assessment of nanomaterials. In general it seems that NanoSafer and Stoffenmanager Nano are suited for inclusion in R.14 (ECHA, 2012b) in order to provide guidance to registrants on how to address and manage NM in a REACH context. Stoffenmanager Nano and NanoSafer, however, focus specifically on inhalation and work is needed to develop CB-nano tools for estimating dermal and oral exposure.

With respect to nano-relevance of the materials to be assessed, the CB-nano tools have different inclusion criteria. For example all tools but the Swiss Precautionary Matrix include a size criterion of maximum diameter of the individual particles, fibers, tubes, and flakes at 100 nm or smaller while the Swiss Precautionary Matrix includes particles up to 500 nm. The difference in size criteria suggest that there is a need to harmonize the definition of the nano-relevance parameter used and to be clear what the including criteria are and how it is defined/measured. Moreover, it is important to take the hazard information into account as recommended also by Hunt et al. (2013) "… integrates rather than separate exposure and toxicity for realistic modelling". In this way an advanced tool is able to analyze if there is a risk and if the risk is not relevant or in which condition the risk is relevant. Therefore it is able to suggest which action is needed to be taken into account at the source, at the receptor and at the compartment level to reduce the exposure and then the risk. Therefore for further development of more generically applicable exposure assessment frameworks, harmonization and calibration of the input parameters and the output is needed to improve the coherency of results and the applicability and the predictions. Identification and harmonization on what can be classified as determinant parameters; e.g.: room size, ventilation exchange rate, activity duration, activity energy, dustiness and humidity influence; is also needed for the evaluation of the potential exposure (Levin et al., 2014). Finally, to enable comparability of results, there is a need to harmonize or calibrate the scaling of the bands. Moreover, if the methods are compiled into a framework, harmonization or calibration of the control bands and their associated risk management suggestions is needed to ensure similar risk communication to the safety professionals and employees expected to have different aims, skills and expertise.

5. Conclusions

The six risk categorization- and control banding tools analyzed here have different application domains and are based on different concepts and output formats: The CB Nanotool was developed for protecting nanotechnology researcher; IVAM Guidance was developed for supporting employee and employers in discussing their workplace safety; Stoffenmanager Nano, NanoSafer, ANSES were developed for occupational risk assessment and management during the production and downstream use; Precautionary Matrix for risk identification and prioritization.

The number of input parameters found to be determinant for the exposure estimations varied from one or two (IVAM Guidance, ANSES) to more than 15, including exposure characterization and control measures (NanoSafer and Stoffenmanager Nano, respectively).

The different tools allocate control bands in different ways with different numbers of control bands and different typologies of recommendation. Some tools (CB Nanotool, ANSES, IVAM Guidance) recommend general risk management, while others (Stoffenmanager Nano and NanoSafer) provide also recommendations for exposure control.

Due to differences in the input parameters and the output format, it is not possible to perform a direct quantitative comparison of their performance and therefore also not possible to immediately combine the different models into a larger holistic framework.

Even-though the evaluated tools were not developed for regulatory use, Stoffenmanager Nano and NanoSafer already include the determinant parameters suggested in ECHA Guidance R.14 and R.14-4, RIPoN-1, RIPoN-2 and thereby principally fulfill REACH requirements for exposure assessment.

Acknowledgments

This work is part of a PhD project under the Danish Centre for Nanosafety founded by the Danish Working Environment Research Foundation (grant number 20110092173/3). The work benefitted from discussions held at the Joint Danish Nanosafety Centre and SUN (EU FP7 project SUN (SUSTAINABLE NANOTECHNOLOGIES (project number 604305)) Control Banding Workshop held at the National Research Centre for the Working Environment on 10-11 October 2013 with participants of Poul Erik Andersen (Danish Working Environment Authority); Derk H. Brouwer (TNO); Maria Hedmer (Labmedicin Skåne); Jurgen Höck (Temas); Ismo Kalevi Koponen (NRCWE); Henrik Vejen Kristensen (Danish Technological Institute); Hanna Landberg (Lund University); Laura MacCalman (IOM); Nanna Rosted Vind (Danish Working Environment Authority); Jody Schinkel (TNO);

Ulla Birgitte Vogel (NRCWE) in addition to the paper authors. We gratefully acknowledge the information exchange with our colleagues during the meeting.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.impact.2016.04.002.

References

Aitken, R.A., Bassan, A., Friedrichs, S., Hankin, S.M., Hansen, S.F., Holmqvist, J., et al., 2011. Specific advice on exposure assessment and hazard/risk characterisation for nanomaterials under REACH (RIP-oN 3). Final Proj Report REACH-NANO Consult-ON3FPR1FINAL (Journal Article).

Asbach, C., Kaminski, H., Fissan, H., Monz, C., Dahmann, D., Mülhopt, S., et al., 2009. Comparison of four mobility particle sizers with different time resolution for stationary exposure measurements. J. Nanoparticle Res. 11 (7), 1593–1609 Oct 1.

Asbach, C., Rating, U., Kuhlbusch, T.A.J., 2014. In: Vogel, U., Savolainen, K., van Wu, Q., Tongeren, M., Brouwer, D., Berges, M. (Eds.), Chapter 4.2 Modeling of the evolution of a nanoparticle aerosol in a simulated workplace; in Chapter 4: From source to dose: Emission, Transport, Aerosoldynamics and Dose assessment for WP aerosol exposure, Handb Nanosafety Meas Expo Toxicol Elsevier, p. 29.

ASTM E2456, 2012. Standard Terminology Relating to Nanotechnology. ASTM International.

Bakand, S., Hayes, A., 2012. Dechsakulthorn finance. nanoparticles: a review of particle toxicology following inhalation exposure. Inhal. Toxicol. Int. Forum Respir. Res. 24 (2), 125–135.

Brouwer, D.H., 2012. Control banding approaches for nanomaterials. Ann. Occup. Hyg. 56 (5), 506–514 Jul.

BS EN 15051, 2006. Workplace atmospheres. Measurement of the dustiness of bulk materials. Requirements and reference test methods [Internet] (Available from: http://shop.bsigroup.com/ProductDetail/?pid=000000000030123370).

Burdett, G., Bard, D., Kelly, A., Thorpe, A., 2013. The effect of surface coatings on the dustiness of a calcium carbonate nanopowder. J. Nanoparticle Res. 15 (1), 1–17.

Cornelissen, R., Jongeneelen, F., van Broekhuizen, F., van Broekhuizen, F., 2011. Guidance working safely with nanomaterials and products, the guide for employers and employees. Amst Neth. (Journal Article).

COSHH, 2002. The technical basis for COSHH essentials: Easy steps to control chemicals [Internet] Available from: www.coshh-essentials.org.uk/assets/live/CETB.pdf.

Dahmann, D., Taeger, D., Kappler, M., Büchte, S., Morfeld, P., Brüning, T., et al., 2007. Assessment of exposure in epidemiological studies: the example of silica dust. J Expo Sci Environ Epidemiol. 18 (5), 452–461.

Dolez, P.I., Bodila, N., Lara, J., Truchon, G., 2009. Personal protective equipment against nanoparticles. Int. J. Nurs. Pract. 15 (6), 99–117.

EC European Commission, 2011. Commission Recommendation of 18 October 2011 on the definition of nanomaterial.

ECHA, 2012a. Guidance on information requirements and chemical safety assessment. Appendix R14-4 Recommendations for nanaomaterials applicable to Chapter R.14 Occupational exposure estimation.

ECHA, 2012b. Guidance on information requirements and chemical safety assessment Document R.14: Occupational exposure estimation.

ETEAM Conference, 2014. The Evaluation of Tier 1 Exposure Assessment Models under Reach ("eteam") project. Federal Institute for Occupational Safety and Health (BAuA) (Available from: http://www.eteam-project.eu/ETEAMConference.aspx).

Faccini, M., Vaquero, C., Amantia, D., 2012. Development of protective clothing against nanoparticle based on electrospun nanofibers. J. Nanomater. 2012, 9.

Fransman, W., Schinkel, J., Meijster, T., Van Hemmen, J., Tielemans, E., Goede, H., 2008. Development and evaluation of an exposure control efficacy library (ECEL). Ann. Occup. Hyg. 52 (7), 567–575.

Hankin, S.M., Peters, S.A.K., Poland, C.A., Foss Hansen, S., Holmqvist, J., Ross, B.L., et al., 2011. Specific advice on fulfilling information requirements for nanomaterials under REACH (RIP-oN 2). Final Proj Rep RNCRIP-ON2FPR1FINAL. Eur. Comm. Jt. Res. Cent. Ispra Italy;(Journal Article).

Höck, J., Hofmann, H., Krug, H., Lorenz, C., Limbach, L., Nowack, B., et al., 2008. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials [Internet] Available from: http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/Spiegel_053/$FILE/Guidelines+on+the+Precautionary+Matrix+for+Synthetic+Nanomaterials+June+09.pdf.

Höck, J., Epprecht, T., Hofmann, H., Höhener, K., Krug, H., Lorenz, C., et al., 2011. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials [Internet] Available from: http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR26/$FILE/Wegleitung_e.pdf.

Höck, J., Epprecht, T., Furrer, E., Gautschi, M., Hofmann, H., Höhener, K., et al., 2013. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials [Internet]. Federal Office of Public Health and Federal Office for the Environment (Available from: http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/NanoSR26/$FILE/Wegleitung_e.pdf).

Hunt, G., Lynch, I., Cassee, F., Handy, R.D., Fernandes, T.F., Berges, M., et al., 2013. Towards a consensus view on understanding nanomaterials hazards and managing exposure: knowledge gaps and recommendations. Materials 6 (3), 1090–1117.

ISO/TS 12901-2, 2014. Nanotechnologies — occupational risk management applied to engineered nanomaterials — part 2: use of the control banding approach [Internet]. International Organization for Standardization (Available from: http://www.iso.org/iso/catalogue_detail.htm?csnumber=53375).

ISO/TS 27687, 2008. Nanotechnologies — terminology and definitions for nano-objects–nanoparticle, nanofibre, and nanoplate [Internet]. International Organization for Standardization (Available from: http://www.iso.org/iso/catalogue_detail?csnumber=44278).

Jensen, K.A., Koponen, I.K., Clausen, P.A., Schneider, T., 2009. Dustiness behaviour of loose and compacted bentonite and organoclay powders: what is the difference in exposure risk? J. Nanoparticle Res. 11 (1), 133–146.

Jensen, K.A., Zalk, D.M., Van Tongeren, M., Bloch, D., de Heer, C., Northage, C., et al., 2010. SAP (Science Advisory Panel): a teleconference was organized by the Stoffenmanager consortium to discuss the proposal for Stoffenmanager Nano. TNO Report.

Jensen, K.A., Saber, A.T., Kristensen, H.V., Liguori, B., Jensen, A.C.Ø., Koponen, I.K., et al., 2016. NanoSafer version 1.1: A web-based precautionary risk assessment and management tool for manufactured nanomaterials using first order modeling (in preparation).

Karlsson, H.L., Gustafsson, J., Cronholm, P., Moller, L., 2009. Size-dependent toxicity of metal oxide particles-a comparison between nano- and micrometer size. Toxicol. Lett. 188 (2), 112–118.

Koivisto, A.J., Aromaa, M., Koponen, I.K., Fransman, W., Jensen, K.A., Mäkelä, J.M., Hämeri, K.J., 2015. Workplace performance of a loose-fitting powered air purifying respirator during nanoparticle synthesis. J. Nanopart. Res 17, 177.

Kristensen, H.V., Hansen, S.V., Holm, G.R., 2010. Nanopartikler i arbejdsmiljøet: Viden og inspiration om håndtering af nanomaterialer [Internet] Available from: http://nanosafer.i-bar.dk/media/Nanopartikler_i_arbejdsmiljoet_samlet.pdf.

Kuhlbusch, T.A., Asbach, C., Fissan, H., Göhler, D., Stintz, M., 2011. Nanoparticle exposure at nanotechnology workplaces: a review. Part. Fibre Toxicol. 8 (1), 22.

Leskinen, J., Joutsensaari, J., Lyyränen, J., Koivisto, J., Ruusunen, J., Järvelä, M., et al., 2012. Comparison of nanoparticle measurement instruments for occupational health applications. J. Nanoparticle Res. 14 (2), 1–16 Jan 26.

Levin, M., 2015. Influence of instruments performance and material properties on exposure assessment of airborne engineered nanomaterials. DTU Nanotech - PhD Thesis [Internet] (Available from http://orbit.dtu.dk/files/116619383/Thesis_mlev_v2.pdf).

Levin, M., Koponen, I.K., Jensen, K.A., 2014. Exposure assessment of four pharmaceutical powders based on dustiness and evaluation of damaged HEPA filters. J. Occup. Environ. Hyg. 11 (3), 165–177.

Levin, M., Gudmundsson, A., Pagels, J.H., Fierz, M., Mølhave, K., Löndahl, J., et al., 2015a. Limitations in the use of unipolar charging for electrical mobility sizing instruments: a study of the fast mobility particle sizer. Aerosol Sci. Technol. 49 (8), 556–565.

Levin, M., Witschger, O., Bau, S., Jankowska, E., Koponen, I.K., Koivisto, A.J., et al., 2015b. Can we trust real time measurements of lung deposited surface area concentrations in dust from powder nanomaterials? Aerosol Air Qual. Res.

Linkov, I., Satterstrom, F.K., Monica, J.C.J., Foss, S., 2009. Nano Risk Governance: Current Developments and Future Perspectives. Nanotechnol Law Bus [Internet]. 6 (Journal Article). Available from http://heinonline.org/HOL/Page?handle=hein.journals/nantechlb6&id=205&div=&collection=.

Maynard, A.D., 2014. A decade of uncertainty. Nat. Nanotechnol. 9 (3), 159–160.

Oberdörster, G., 2002. Toxicokinetics and effects of fibrous and nonfibrous particles. Inhal. Toxicol. 14 (1), 29–56.

Oberdörster, G., Maynard, A., Donaldson, K., Castranova, V., Fitzpatrick, J., Ausman, K., et al., 2005. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part. Fibre Toxicol. [Internet] 2 Oct 6;Available from: //MEDLINE:16209704.

OECD, . Safety of manufactured nanomaterials [Internet] [cited 2015]. May 26 Available from: http://www.oecd.org/env/ehs/nanosafety/.

Oomen, A.G., Bleeker, E.A.J., Bos, P.M.J., van Broekhuizen, F., Gottardo, S., Groenewold, M., et al., 2015. Grouping and read-across approaches for risk assessment of nanomaterials. Int. J. Environ. Res. Public Health 12 (10), 13415–13434 Oct 26.

Ostiguy, C., Riediker, M., Triolet, J., Troisfontaines, P., Vernez, D., 2010. Development of a specific control banding tool for nanomaterials. Expert Comm CES Phys Agents French Agency Food Environ Occup Health Saf Maisons-Alfort Cedex (Journal Article).

Paik, S.Y., Zalk, D.M., Swuste, P., 2008. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Ann. Occup. Hyg. 52 (6), 419–428.

Park, J., Kwak, B., Kim, Y., Yi, J., 2011. Efficiency of protective dermal equipment against silver nanoparticles with water aerosol. J. Nanoparticle Res. 13 (7), 3043–3049 Jul 1.

PEROSH, 2014. Exposure measurements and risk assessment of manufactured materials/nanoparticles (MMNPs). Project B: Nano Exposure and Contextual Information Database (NECID). PEROSH (Available from: http://www.perosh.eu/development-of-a-nano-exposure-and-contextual-information-database-necid/).

Rengasamy, A., Zhuang, Z., BerryAnn, R., 2004. Respiratory protection against bioaerosols: literature review and research needs. Am. J. Infect. Control 32 (6), 345–354.

Riediker, M., Ostiguy, C., Triolet, J., Troisfontaine, P., Vernez, D., Bourdel, G., et al., 2012. Development of a control banding tool for nanomaterials. J. Nanomater. 8 Journal Article.

Safe Work Australia, 2010. Engineered Nanomaterials: Feasibility of establishing exposure standards and using control banding in Australia [Internet]. Safe Work Australia (Available from: http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/at201008workhealthandsafetyassessmenttool).

SCENIHR, 2010. Opinion on the scientific basis for the definition of the term "nanomaterial" [Internet]. European Union 2010 (Dec Report No.: 978-92-79-12757-1. Available from http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf).

Schneider, T., Jensen, K.A., 2008. Combined single-drop and rotating drum dustiness test of fine to nanosize powders using a small drum. Ann. Occup. Hyg. 52 (1), 23–34.

Schneider, T., Brouwer, D.H., Koponen, I.K., Jensen, K.A., Fransman, W., Van Duuren-Stuurman, B., et al., 2011. Conceptual model for assessment of inhalation exposure to manufactured nanoparticles. J Expo Sci Environ Epidemiol. 21 (5), 450–463.
Schulte, P.A., Geraci, C.L., Hodson, L.L., Zumwalde, R.D., Kuempel, E.D., Murashov, V., et al., 2013. Overview of risk Management for engineered nanomaterials. J. Phys. Conf. Ser. 429 (1), 012062.
Seipenbusch, M., 2014a. In: Vogel, U., Savolainen, K., van Wu, Q., Tongeren, M., Brouwer, D., Berges, M. (Eds.), Chapter 4.4.1 Sources of Nanoparticles in the Work Place; in Chapter 4: from Source to Dose: Emission, Transport, Aerosoldynamics and Dose Assessment for WP Aerosol Exposure, Handb Nanosafety Meas Expo Toxicol Elsevier.
Seipenbusch, M., 2014b. In: Vogel, U., Savolainen, K., van Wu, Q., Tongeren, M., Brouwer, D., Berges, M. (Eds.), Chapter 4.4.2 Aerosol Dynamics in Workplace Atmospheres; in Chapter 4: from Source to Dose: Emission, Transport, Aerosoldynamics and Dose Assessment for WP Aerosol Exposure, Handb Nanosafety Meas Expo Toxicol Elsevier.
Shaffer, R., Rengasamy, S., 2009. Respiratory protection against airborne nanoparticles: a review. J. Nanoparticle Res. 11 (7), 1661–1672 Oct 1.
Stone, V., Pozzi-Mucelli, S., Tran, L., Aschberger, K., Sabella, S., Vogel, U., et al., 2014. ITS-NANO — Prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy. Part Fibre Toxicol. 11, 9–11 (Journal Article).
Studer, C., Furrer, E., Höck, J., 2013. Leaflet on the Precautionary Matrix for Synthetic Nanomaterials [Internet] Available from http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwallbykey/nano_vorsorgeraster_doc|en.
Van Duuren-Stuurman, B., Vink, S.R., Verbist, K.J., Heussen, H.G., Brouwer, D.H., Kroese, D.E., et al., 2012. Stoffenmanager Nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. Ann. Occup. Hyg. 56 (5), 525–541.
Warheit, D.B., 2008. How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization? Toxicol. Sci. 101 (2), 183–185.
Warheit, D.B., Sayes, C.M., Reed, K.L., Swain, K.A., 2008. Health effects related to nanoparticle exposures: environmental, health and safety considerations for assessing hazards and risks. Pharmacol. Ther. 120 (1), 35–42.
WHO/EURO, 1985. Reference methods for measuring airborne man-made mineral fibres (MMMF). Copenhagen: WORLD HEALTH ORGANIZATION, p. 55.
Zalk, D.M., Paik, S.Y., 2010. Control Banding and Nanotechnology. Synergist Mar 10 03/10:age.
Zalk, D.M., Paik, S.Y., Swuste, P., 2009. Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J. Nanoparticle Res. 11 (7), 1685–1704.